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Single-cell transcriptome and genome analysis: A much-needed tool for pituitary neuroendocrine tumor studies

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See article by Cui et al. pp 1859–1871

> Students who would enter in to the field of endocrine,
> tread with caution, best be wary of the gland pituitary.
> Quartered squarely in the head of the pit, it can be said,
> as a metabolic proctor, it outsmarts the smartest doctor.
> (*The New England Journal of Medicine*)

The pituitary gland, considered to be the "master" gland because of its importance in regulating hormonal function, is a tiny but powerful structure located at the base of the brain. Tumors of this gland are increasingly recognized.[1] Our understanding of the cytogenesis of tumors derived from adenohypophysial cells has grown exponentially. Initially, hormone production was paramount[2]; the current complex classification is based on cell lineage as defined by expression of transcription factors, patterns of hormone production, and additional measures of cytodifferentiation shown by other features such as keratins and E-cadherin.[1] The role of genetic and epigenetic regulators in tumorigenesis has expanded the spectrum of pathogenetic factors beyond the known familial predisposition genes.[3] As in other tumors, studies of genomic and proteomic profiling have been attempted to further clarify the characteristics of these increasingly common and complex lesions.[4] However, the nature of the pituitary and its tumors is so complex that it remains true indeed that the pituitary outsmarts the brightest and best investigators.[5]

In the study by Cui et al, "Single-cell transcriptome and genome analyses of pituitary neuroendocrine tumors,"[6] the authors have successfully addressed one of the major limitations of previous studies. In fact, the pituitary is a complex gland composed of at least 6 different hormone-producing cell types in addition to the usual panoply of stromal and vascular cells, including in this case unusual S100-positive sustentacular cells. Tumors in this tiny gland grow by gradually infiltrating around nontumorous tissue, trapping nontumorous elements.[7] Thus traditional studies using pieces of tissue, despite claims of being "morphologically characterized as tumor," are usually contaminated with nontumorous cells that can skew the results of these meticulous analyses,[5] leading to incorrect results. In this landmark study, using high-precision single-cell RNA sequencing, Cui et al analyzed 2679 individual cells obtained from 23 surgically resected samples of the major subtypes of PitNETs from 21 patients. They then proceeded to perform single-cell multi-omics sequencing on 238 cells from 5 patients. This study shows the precision required to properly identify the features of tumor cells that may be a homogeneous population but may also be heterogeneous.[1]

This study has identified that differentially expressed genes of gonadotroph tumors are predominantly downregulated, while those of somatotroph and lactotroph tumors are mainly upregulated and they also identified that plurihormonal tumors show little transcriptomic heterogeneity; this is a fascinating result that correlates with what clinicians have recognized for many years about the distinctions between functioning and nonfunctioning PitNETs. This study also identified novel genes that may be implicated in pituitary tumorigenesis, including *AMIGO2*, *ZFP36*, *BTG1*, and *DLG5*, potentially opening the door to new avenues for investigation of pathogenesis and therapy for aggressive PitNETs.

The approach used by Cui et al is to be commended, as it takes into account the complexity of the structure under investigation before applying expensive and time-consuming technology. It serves as a model for much-needed translational studies of this important gland that will allow progress in a field that has been mired in contradictory and confusing data.

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